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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,126	02/22/2002	Gerald W. DeVries	P-AR 4951	8539

7590 10/08/2004

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,126	DEVRIES, GERALD W.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/15/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-10,15 and 26-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10,15 and 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 8-10, 15, and 26-38 are pending.

2. In view of the amendment filed 7/15/04, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-10, 15, and 26-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising a vascular endothelial growth factor receptor-3 kinase inhibitor selected from the group consisting of 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) and 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51), (2) The said method further comprising administering to said patient an anti-angiogenic agent or an immunosuppressive agent, **does not** reasonably provide enablement for (1) a method of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising *any* "VEGFR-3 kinase inhibitor", *any* VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, *any* VEGFR-3 kinase inhibitor is any "ATP analog", or *any* "VEGFR-3 kinase inhibitor that drown regulates VEGFR-3 expression", (2) the said method further comprises administering to said patient *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", wherein the pharmaceutical composition is administered prior to, or subsequent to corneal transplantation, two or more times, over a period of at least one or six months as set forth in claims 8-10, 15, and 26-38. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structures as shown on page 56 and a method of extending corneal graft survival in a rat model of karetoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51). The specification discloses that transplantation of corneas from Lewis strain rats to Wistar-Furth recipients, where rats receiving only vehicle demonstrate evidence of graft rejection, on average, at day 30. In contrast, in animals receiving MAE87, MAE106 or MAZ51 exhibit increased mean graft survival as demonstrated by a significant delay in evidence of graft rejection.

The specification does not teach how to make all "VEGFR-3 kinase inhibitor" such as "VEGFR-3 kinase inhibitor" that binds to the VEGFR-3 catalytic domain, any ATP analog, any VEGFR-3 kinase inhibitor that down regulates VEGFR-3 expression for the claimed method of extending corneal graft survival following corneal transplantation in a human. The specification does not teach how to make any inhibitor mentioned above because there is insufficient guidance as to the structure without the amino acid sequence, or chemical structure of *all* "VEGFR-3 kinase inhibitor" such as *all* "ATP analog", or *any* "VEGFR-3 inhibitor drown regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", let alone which undisclosed ATP analog would bind to VEGFR-3 catalytic domain and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the indefinite number of undisclosed VEGFR-3 kinase inhibitor, there is insufficient guidance as to which conformational changes and amino acids contact with the VEGFR-3 are responsible for inhibiting lymphangiogenesis, ATP binding and/or tyrosine kinase phosphorylation. Further, there is insufficient in vivo working example demonstrating that all VEGFR-3 kinase inhibitor are effective for extending corneal graft survival. Given the indefinite number of undisclosed VEGFR-3 inhibitor, it is unpredictable which undisclosed inhibitor has which particular function such as binding to the VEGFR-3 catalytic domain, down regulating VEGFR-3 expression and/or tyrosine kinase phosphorylation. Until the VEGFR-3 receptor kinase inhibitor has been identified, the specification as filed merely invites one of skill in the art for further experimentation to arrive at the scope of the claimed invention. Since the VEGFR-3 kinase inhbitor, and ATP analog in the claimed method are not enabled, it follows that the said method further comprising any undisclosed anti-angiogenic agent, or immunosuppressive agent is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/15/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification provides sufficient guidance regarding how to make and use the invention with a variety of VEGFR-3 kinase inhibitors including, but not limited to, MAE87, MAE 106 and MAZ51. As additional guidance to the skilled person regarding how to make and use the claimed invention, the specification teaches that one skilled in the art can identify additional VEGFR-3 kinase inhibitors using routine techniques. In this regard, the specification teaches a well-known assay for identifying VEGFR-3 kinase inhibitors by detecting production of phosphorylated tyrosine with anti-phosphotyrosine antibody. As guidance to the skilled person, an exemplary protocol for detection of phosphorylated tyrosine by ELISA is set forth in the specification at page 22, lines 1-24; such assays are routine and well known in the art, as described, for example, in Hermequin et al., J. Med. Chem. 42:5369-5389 (1999), and Wedge et al., Cancer Res. 60:970-975 (2000), which are incorporated into the specification (page 21, line 27, to page 22, line 1; and page 57, lines 14-17). Briefly, one skilled in the art can incubate a potential inhibitor with the VEGFR-3 cytoplasmic receptor domain in an appropriate buffer in the presence of ATP, with subsequent detection of phosphorylated tyrosine using a commercially available anti-phosphotyrosine antibody (page 22, lines 6-19). A reduction in the amount of phosphorylated tyrosine in the presence of the proposed kinase inhibitor, as compared to the amount of phosphorylated tyrosine in the absence of the proposed inhibitor, indicates kinase inhibitory activity. Thus, using the guidance in the specification, one skilled in the art would have been able to use well-known methods to screen for, or corroborate the activity of, VEGFR-3 kinase inhibitors. Applicant respectfully points out that it is not necessary to describe a mechanism of action in order to teach how to make and use the invention. As set forth above, kinase inhibitory activity can be identified or corroborated without knowledge of the inhibitor-receptor contacts. Applicant need not demonstrate that all VEGFR-3 kinase inhibitors would function to extend corneal graft survival in the methods of the invention. Rather, it is well established that claims are permitted to encompass inactive embodiments. The Examiner has not provided any evidence or reasoning as required under MPEP 2164.04 as to why one skilled in the art would expect some, but not all, VEGFR-3 kinase inhibitors to inhibit lymphangiogenesis and, thus, to extend corneal graft survival. Without evidence or specific reasoning to the contrary, one skilled in the art would have understood that the highly conserved tyrosine kinase domain of VEGFR-3 (see page 12, lines 14-17) was critical to activity of the receptor and would have expected that a variety of VEGFR-3 kinase inhibitors would disrupt the activity of VEGFR-3, including its lymphangiogenic activity, as taught in the subject application.

Applicants' arguments filed 7/15/04 have been fully considered but are not found persuasive.

The scope of the claims encompasses a method of extending corneal graft survival following corneal transplantation by administering a pharmaceutical composition comprising any VEGFR-3 kinase inhibitor, any VEGFR-3 inhibitor that binds to the catalytic domain of VEGFR-3 such as any ATP analog, any VEGFR3 inhibitor that down-regulates VEGFR-3 expression.

However, the specification does not teach how to make all "VEGFR-3 kinase inhibitor" such as "VEGFR-3 kinase inhibitor" that binds to the VEGFR-3 catalytic domain, any ATP analog, any VEGFR-3 kinase inhibitor that down regulates VEGFR-3 expression for the claimed method of extending corneal graft survival following corneal transplantation in a human. The specification does not teach how to make any inhibitor mentioned above because there is insufficient guidance as to the structure without the amino acid sequence, or chemical structure of *all* "VEGFR-3 kinase inhibitor" such as *all* "ATP analog", or *any* "VEGFR-3 inhibitor drown regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", let alone which undisclosed ATP analog would bind to VEGFR-3 catalytic domain and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) for the claimed method of extending corneal graft survival. Given the indefinite number of VEGFR-3 kinase inhibitor that selectively or non-selectively reduces the tyrosine kinase activity of VEGFR-3 without significantly effecting the expression of VEGFR-3 as defined on page 20 of specification, it is not routine to one skilled in the art to extend corneal graft by administering any undisclosed VEGFR-3 kinase inhibitor as asserted by applicant.

Until the specific VEGFR-3 kinase inhibitor has been identified, the specification merely extends an invitation to one skilled in the art to use well-known methods to screen for, or corroborate the activity of, VEGFR-3 kinase inhibitors to the claimed method. In contrast to

applicant's assertion that one skilled in the art could make and use the claimed invention by incubating a potential inhibitor with the VEGFR-3 cytoplasmic receptor domain in an appropriate buffer in the presence of ATP, with subsequent detection of phosphorylated tyrosine using a commercially available anti-phosphotyrosine antibody (page 22, lines 6-19), in vitro assay does not correlate with in vivo activity since the therapeutic indices of pharmaceutical drug can be species- and model-dependent. VEGFR-3 kinase inhibitor in the absence of in vivo data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). As evidence by Traxler et al (Exhibit A) who shows that currently there are more than 20 different tyrosine kinase targets and some of these tyrosine kinase inhibitors that had to be withdrawn from development due to insufficient physiochemical properties such as ZD4190 or insufficient efficacy in patients such as SU5416 or due to liver toxicity BIBX1382BS and PKI166 (See page 227, in particular). Engh et al as evident on page 21 of the specification (See enclosed Exhibit B for Applicant's convenient) who summarizes that clearly more crystal structures of other inhibitor complexes are needed to complete our understanding of the binding parameters in the ATP-binding sites of protein kinases (See page 26163, col. 2, last paragraph, in particular). Finally, as evidence by Plskova et al (Exhibit C) who teaches that there are many components contribute to rejection of corneal graft such as opacification or reduced clarity of the cornea including cellular infiltration, new vessel ingrowth, thickening and irregularity of the cornea, edema, host MHC genetic background and surgical trauma (See page 108, in particular). In both rats and mice, almost all animals pass through an early phase (8-21 days post graft) in which the corneal opacity grade reaches a level greater than clinical grade where the donor cornea is clinically rejected but that in some strain combinations, there is potential recovery of corneal clarity at a later stage, generally taken as 8 weeks post graft. Plskova et al further teach that the eventual "success" or "failure" of a graft can only be judged by a combination of the level of opacity of the graft and a specific duration (See page 112, col. 1, in particular). Given the numerous factors contributing to the extending corneal

graft survival and the insufficient guidance as to structure of all VEGFR-3 inhibitors, the specification does not reasonably provide sufficient data to show all VEGFR-3 kinase inhibitors that either selectively or non-selectively reduces the tyrosine kinase of a VEGF-3 receptor as defined by the specification on page 20 could extend corneal graft survival by inhibiting allograft vascularization. In fact, Kirkin et al, of record, teach that it should borne in mind that interpretation of results in more complex systems may be difficult for if VEGFR-3 inhibitor MAE106 or MAZ51 also inhibit other receptor tyrosine kinases (RTKs) (See page 5538, col. 2, first paragraph, in particular).

5. Claims 8-10, 15, and 26-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all "vascular endothelial growth receptor-3 (VEGFR-3) kinase inhibitor such as any VEGFR-3) kinase inhibitor is any ATP analog, any VEGFR-3 kinase inhbitor that binds the VEGFR-3 catalytic domain, and any VEGFR-3 kinase inhibitor that down regulates VEGFR-3 expression for the claimed method as set forth in claims 8-10, 15, and 26-38.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of karetenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) that extends corneal graft survival in rat.

The specification defines the term "VEGFR-3 kinase inhibitor" means an inhibitor of receptor tyrosine kinase that selectively or non-selectively reduces the tyrosine kinase of a VEGF-3 receptor such as an inhibitor that reduces VEGFR-3 tyrosine kinase activity without significantly effecting VEGFR-3 expression or other VEGFR-3 activity (page 20). The VEGFR-

3 kinase inhibitor can be any molecule that directly binds the VEGFR-3 catalytic domain, such as ATP analog. However, binding does not equal to function.

With the exception of the specific inhibitors of VEGFR-3 for the claimed method of extending corneal graft, there is insufficient written description about the structure associated with function of all inhibitors mentioned above without the specific amino acid sequence or the specific chemical structure, let alone any molecule that binds to the VEGFR-3 catalytic domain, or any ATP analog has which particular function such as inhibiting tyrosine kinase phosphorylation, or ATP binding activity or inhibiting VEGFR-3 expression. Since the VEGFR-3 kinase inhbitor, ATP analog, and VEGFR-3 kinase inhibitor that down regulates VEGFR-3 for the claimed method are not adequately described, it follows that the said method further comprising any undisclosed anti-angiogenic agent, or immunosuppressive agent is not adequately described.

The specification discloses only three specific VEGFR-3 kinase inhibitors that extend corneal graft rejection. Given the lack of any additional species of "VEGFR-3 kinase inhibitor" such as "ATP analog", and "VEGFR-3 inhibitor drown regulates VEGFR-3 expression" for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/15/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification describes the genus of VEGFR-3 kinase inhibitors in such a way as to reasonable convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. In this regard, the specification describes a VEGFR-3 inhibitor as an inhibitor of receptor tyrosine kinase activity that selectively or non-selectively reduces tyrosine kinase activity of a VEGFR-3 receptor (page 20, lines 24-28). The specification further describes structural and functional characteristics of the recited genus of VEGFR-3 kinase inhibitors. As set forth in the specification, a VEGFR-3 kinase inhibitor useful in the invention can have the structure, for example, of an ATP analog, or can

have the function of binding the VEGFR-3 catalytic domain (page 21, lines 1-13). Members of the genus of VEGFR-3 kinase inhibitors are further functionally characterized in the specification by the ability to reduce production of phosphorylated tyrosine as determined by ELISA assay using a mouse IgG anti-phosphotyrosine antibody (page 21, line 27, to page 22, line 24). Additional written description is provided by the disclosure of MAE87, MAE 106 and MAZ51 and their structures as exemplary species of VEGFR-3 kinase inhibitor (page 21, lines 14-21; page 56). The specification also provides sufficient written description for the genus of anti-angiogenic agents. As set forth at page 41, lines 3-10, the specification describes an anti-angiogenic agent as a molecule that reduces or inhibits angiogenesis, which is the formation of new blood vessels. In the methods of the invention, an anti-angiogenic agent is optionally administered in conjunction with a VEGFR-3 inhibitor (page 40, line 24, to page 41, line 2). The specification further provides written description for the genus of anti-angiogenic agents by disclosing a variety of exemplary species including, for example, angiostatin, endostatin, metastatin, and 2ME2; anti-VEGF antibodies such as Avastin', and VEGFR-2 inhibitors such as 5U5416 and 5176618 (page 43, lines 9-23). The specification discloses a variety of exemplary immunosuppressive agents including corticosteroids and other steroids such as prednisolone acetate, cyclosporine and tacrolimus (FK506), and therapeutic monoclonal antibodies including anti-T lymphocyte, anti-CD4+ cell, anti-ICAM-l and anti-IL-2 antibodies (page 44, line 1, to page 45, line 4).

However, the scope of the claims encompasses a method of extending corneal graft survival following corneal transplantation by administering a pharmaceutical composition comprising any VEGFR-3 kinase inhibitor, any VEGFR-3 inhibitor that binds to the catalytic domain of VEGFR-3 such as any ATP analog, any VEGFR3 inhibitor that down-regulates VEGFR-3 expression.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of karetenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one

(MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) that extends corneal graft survival in rat.

The specification provides neither a representative number of VEGFR-3 kinase inhibitors to described the claimed genus, nor does it provide a description of the structural features that are common to VEGFR-3 kinase inhibitors. As discussed above, the specification provides no structural description of VEGFR-3 kinase inhibitor other than the ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure for themselves what the VEGFR-3 kinase inhibitor for the claimed method look like. Since the VEGFR-3 kinase inhibitor for the claimed method is not adequately described, the method further comprising administering the "anti-angiogenic agent", or "immunosuppressive agent" is not adequately described.

6. The following new ground of rejection is necessitated by the amendment filed 7/15/04.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "said VEGFR-3 inhibitor" in claim 15 has no antecedent basis in base claim 8 because the word "VEGFR-3 inhibitor" is not recited in claim 1.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
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September 30, 2004

Christina Chan
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